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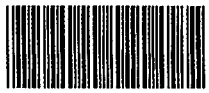

Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization Based on Emerging Information

Notice

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

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EXECUTIVE SUMMARY

The purposes of this document is to present an assessment that updates previous provisional values issued by the U.S. Environmental Protection Agency (EPA) for an oral reference dose (RfD) for perchlorate, to evaluate the potential for perchlorate carcinogenicity, and to provide a screening ecological risk assessment for perchlorate based on toxicity data that recently have become available. Most of these data were obtained as results of a testing strategy that was designed with knowledge of the mode of action for perchlorate toxicity that identified major data gaps in the data available prior to 1997. This executive summary concisely presents key findings from the present assessment.

SUMMARY FINDINGS

Sources of Perchlorate Contamination and Occurrence

- Perchlorate is an oxidizing anion that originates as a contaminant in ground and surface waters from the dissolution of ammonium, potassium, magnesium, or sodium salts. Perchlorate is exceedingly mobile in aqueous systems and can persist for many decades under typical ground and surface water conditions.
- Ammonium perchlorate is manufactured for use as the oxidizer component and primary ingredient in solid propellant for rockets, missiles, and fireworks. Because it is a reducing agent, it can undergo a variety of intramolecular redox reactions that lead to the release of gaseous products, and, thus, it can act as a thrust booster. Perchlorate salts also are used on a large scale as a component of air bag inflators.
- Other uses of perchlorate salts include their use in nuclear reactors and electronic tubes, as additives in lubricating oils, in tanning and finishing leather, as a mordant for fabrics and dyes, in electroplating, in aluminum refining, and in rubber manufacture, as a mordant for fabrics and dyes, and in the production of paints and enamels. Chemical fertilizer also has been reported to be a potential source of perchlorate contamination.
- Large-scale production of perchlorate-containing chemicals in the United States began in the mid-1940s. Because of its shelf life, perchlorate must be washed out of the United States'

missile and rocket inventory to be replaced with a fresh supply. Thus, large volumes have been disposed of in various states since the 1950s.

- Perchlorate began to be discovered at various manufacturing sites and in well water and drinking water supplies within the months following the April 1997 development of a low-level (4 ppb) detection method. There are 14 states with confirmed releases in ground or surface water. There are 44 states that have confirmed perchlorate manufacturers or users based on EPA Information Request responses. In California, most of the locations where perchlorate has been detected are associated with facilities that have manufactured or tested solid rocket fuels for the Department of Defense or the National Aeronautics and Space Administration.
- At this time, there has not been a systematic national survey of perchlorate occurrence. Identification of the magnitude and extent of perchlorate occurrence in the environment is important in assessing the routes of exposure to humans and to determining the different types of organisms and ecosystems that may be affected.

An Integrated Approach to Comprehensive Risk Characterization

- Perchlorate is of concern because of existing uncertainties in the toxicological database available to adequately address the potential for perchlorate to produce human health effects at low levels in drinking water; the actual extent of the occurrence of perchlorate in ground and surface waters, which is compounded by some uncertainty in the validation of the analytical detection method; the efficacy of different treatment technologies for various water uses, such as drinking water or agricultural application; and the extent and nature of ecological impact or transport and transformation phenomena in various environmental media.
- To adequately and comprehensively characterize the risk of perchlorate contamination to provide scientific input to decision making regarding management strategies to mitigate potential risk, a number of key pieces of information are necessary. Accurate characterization of exposures relies on reliable analytical methods. The exposure estimates cannot be gauged with respect to their risk unless robust health and ecological risk estimates are available. Treatment technologies should be targeted to levels of concern and tailored to the intended water use. Technology transfer is necessary so that all affected parties and concerned citizens

are apprised of accurate and reliable information that is up to date with the evolving state of the science.

- The toxicity testing strategy was expedited through a unique partnership between the Department of Defense and EPA, together with members of an Interagency Perchlorate Steering Committee (IPSC), which also includes other governmental representatives from the Agency for Toxic Substances and Disease Registry and the National Institute for Environmental Health Sciences and affected state, tribal, and local governments.
- The charter of the IPSC is to facilitate and coordinate accurate accounts of related technological issues (occurrence surveys, health assessment, ecotoxicology assessment, treatability, waste stream handling, and analytical detection). This assessment is intended to address the need for evaluation of perchlorate's potential to cause human health effects or impact on ecological systems, based on currently available and emerging data.
- There is currently no National Primary Drinking Water Regulation for perchlorate. Perchlorate was placed on the Contaminant Candidate List in March 1998. The list serves as the source for priority contaminants, defined as either known or anticipated to occur in public water systems, for research, guidance development, and selection of contaminants for making regulatory determinations or monitoring by the states. Perchlorate was listed as a contaminant that required additional research and occurrence information before regulatory determinations could be considered.

Physicochemical Characteristics

- As an oxidant, perchlorate is kinetically nonlabile. This means the reduction of the central chlorine atom from an oxidation state of +7 (perchlorate) to -1 (chloride ion) occurs extremely slowly. Sorption is not expected to attenuate perchlorate because it absorbs weakly to most soil minerals. Natural chemical reduction in the environment is not expected to be significant. These two factors account for perchlorate being both very mobile in aqueous systems and persistent for many decades under typical ground and surface water conditions.
- The activation energy to perchlorate reduction is so high that it cannot be expected to act as an oxidant under human physiological conditions (i.e., dilute solution, unelevated temperatures, neutral pH). This is supported by absorption, distribution, metabolism, and elimination studies that show perchlorate is excreted virtually unchanged in the urine after absorption.

Hazard Identification and Mode of Action Testing Strategy

- The health effects and toxicity database available in the spring of 1997 was determined to be inadequate for quantitative risk assessment. A testing strategy was developed based on a hazard identification using the available data and the suspected mode of action for perchlorate to target testing on potential effects of perchlorate.
- Perchlorate is readily absorbed from the intestinal tract, and oral uptake is considered to be the major route of exposure. Because of its high charge, perchlorate does not pass readily through the skin. Exposure via inhalation is expected to be negligible because the vapor pressure of perchlorate salts and acids is expected to be low at room temperatures. Droplet size during showering likely would preclude inhalation of perchlorate contaminated water as an aerosol.
- Perchlorate is known to inhibit the uptake of iodide in the thyroid, thereby causing a reduction in the hormones thyroxine (T3) and triiodothyronine (T4). When these hormones enter the blood circulation, they are bound to plasma proteins. Differences in plasma protein binding between rats and humans account for differences in the circulating half-life of the hormones and in thyroid structure between the species. There may be other locations of inhibition of iodide transport in the gland, but perchlorate itself is not metabolized in the thyroid or peripheral tissues.
- Control of the circulating concentrations of these hormones is regulated primarily by a negative feedback involving three organs (1) the thyroid, which produces T4 and T3, and (2) the pituitary gland and (3) the hypothalamus, which respond to and help maintain optimal T4 and T3 levels by what is known as the hypothalamic-pituitary-thyroid axis or feedback system. The hypothalamus stimulates the pituitary gland through thyrotrophic-releasing hormone (TRH) to produce thyroid stimulating hormone (TSH), which then prompts the thyroid to produce T4 and T3. Cells in the hypothalamus and pituitary gland respond to the levels of circulating T4 and T3, such that, when thyroid production levels are low, there is a signal to increase the output of TRH and TSH. Circulating hormone levels (T4, T3, and TSH) can be monitored readily to serve as biomarkers of exposure and effect of agents that disrupt the status of this negative feedback system.
- Potential effects of perchlorate, given its mode of action as an inhibitor of iodide uptake that results in disturbances of the hypothalamic-pituitary-thyroid axis, included concerns for carcinogenic, neurodevelopmental, developmental, reproductive, and immunotoxic effects.

Additionally, no study had ever evaluated the potential for other systemic effects. Further, there was concern for ecotoxicology effects on various aquatic and terrestrial plants and animals.

- The human health testing strategy included eight different recommended studies to address data gaps and enhance the mechanistic information on the mode of action to provide a comprehensive database on which to arrive at a revised human health risk assessment with greater confidence than previous provisional values. These studies are described below.
  (1) A 90-day oral bioassay to identify other target tissues in young adult rats; to provide data on the effects of repeated exposures to perchlorate on T3, T4, and TSH levels; to evaluate recovery of effects after 30 days; and to screen for some reproductive parameters. A genotoxicity assay also was performed on rats from the terminal sacrifice.
  (2) A neurodevelopmental study in rats to evaluate the potential for functional and morphological effects in offspring from the mother exposed during pregnancy and lactation.
  (3) A Segment II developmental study in rabbits to evaluate the potential for perchlorate to cause birth defects and to provide data on thyroid hormone effects in a second species other than the rat.
  (4) A two-generation reproductive toxicity study to evaluate the potential for perchlorate to cause deficits in reproductive performance in adult rats and for toxicity in the young offspring.
  (5) Absorption, distribution, metabolism, and elimination (ADME) studies to characterize the pharmacokinetics of perchlorate in laboratory animals and humans and to provide data necessary to allow construction of models for quantitative description of different internal dose metrics and interspecies extrapolation.
  (6) Mechanistic studies that characterize the effects of perchlorate on the iodide uptake mechanism across species as a link with the ADME studies to aid in the quantitative extrapolation of dose across species.
  (7) Genotoxicity assays to evaluate the potential for carcinogenicity by evaluating the potential for direct effects on deoxyribonucleic acid.
  (8) Immunotoxicity studies to evaluate the potential for perchlorate to disrupt immune function.

- A battery of ecological screening tests was conducted in laboratory organisms representative of ecological receptors across soil, sediment, and water to evaluate dose-response relationships. These were considered to be a tier of tests to give an idea of gross toxicity that would determine the need for and types of tests to be performed in the next tier. The tests did not measure the amount of perchlorate in the tissues of the species being tested. Based on stakeholder input and the need for a more focused battery of tests, the following species were selected for the first round of testing. Lettuce was substituted for duckweed because of tribal concerns regarding the sizable lettuce crop along the Colorado river.
  (1) *Daphnia magna* (water flea) to represent an aquatic invertebrate
  (2) *Ceriodaphnia magna* (water flea) to represent an aquatic invertebrate
  (3) *Lactuca sativa* (lettuce) to represent a vascular plant
  (4) *Pimephales promelas* (fathead minnow) to represent an aquatic invertebrate
  (5) *Eisenia foetida* (earthworm) to represent a soil invertebrate
  (6) *Microtus pennsylvanicus* (meadow vole) to represent an herbivore
  (7) Frog Embryo Teratogenesis Assay: *Xenopus*
  (8) Phytoremediation study to examine uptake, distribution, and degradation in experimental systems with rooted cuttings of woody plants, including willow, Eastern Cottonwood, and eucalyptus.

Human Health Assessment

- The testing strategy confirmed that the target tissue for perchlorate toxicity was the thyroid gland, as indicated by both perturbations of T3, T4, and TSH hormones and by thyroid histopathology in both adult and postnatal rats. The hormone effects occurred at the lower range of exposures tested, from 0.01 to 1.0 mg/kg-day, whereas the histopathology typically occurred at higher doses, with the exception of follicular epithelial cell hyperplasia observed in rat pups on Postnatal Day 5 (PND5) and in a 14-day study of young rats. Neurobehavioral effects and effects in the brains of offspring occurred at higher concentrations. Preliminary data on reproductive parameters and immunotoxicity indicate potential for an effect.
  No effects were observed in rabbits of the developmental study.
- Thyroid tumors were observed in previous studies in rats exposed in long-term bioassays at high doses. Perchlorate was not found to be genotoxic in any assay of the genotoxicity battery,

although repeated experiments have been requested for two assays. The preliminary data on these repeated studies confirm the lack of genotoxicity by perchlorate.

- Because of strong correlations between changes in T3 and T4 with changes in TSH and between changes in T3, T4, or TSH with thyroid histopathology, an assessment model was proposed that used the changes in T3, T4, and TSH as the precursor lesions to subsequent effects on thyroid hyperplasia that potentially could lead to thyroid tumors or to altered neurodevelopment. This assessment approach essentially harmonizes noncancer and cancer approaches because it is presumed that the no-observed-adverse-effect-level (NOAEL) for the precursor lesion will preclude any subsequent sequelae at higher doses.
- The rat model is considered relevant yet conservative for human health risk assessment of potential thyroid neoplasia because of the differences in thyroid structure and hormone half-lives, as described, so that rats appear to be more sensitive to thyroid cancer caused by thyroid-pituitary disruption. This approach requires demonstration that the indirect disruption is the only mode of action, and that the chemical is not genotoxic. Adverse noncancer thyroid effects, such as thyroid enlargement and histopathology, are presumed to pose a human noncancer health hazard. Perchlorate was demonstrated to be nongenotoxic in the testing battery employed, suggesting the indirect mode of action for potential tumor formation.
- The revised RfD, assumed also to be protective on potential carcinogencity was derived using effects in thyroid histopathology observed in pups on PND5 in the neurodevelopmental study at 0.1 mg/kg-day. The effects in the thyroids of the rat pups at lower levels than in the mother were corroborated by effects in pups of previous studies of guinea pigs and rabbits.

A composite uncertainty factor of 100 was used to address uncertainties resulting from data gaps because of pending studies and for extrapolation of a minimal lowest-observed-adverse-effect level (LOAEL) and intrahuman pharmocodynamic differences and for interspecies differences. Because the test article was ammonium perchlorate, an adjustment factor of 0.85 also was made for the percent of molecular weight of the salt from ammonium (15.35%), so that the RfD is expressed for perchlorate as the anion alone. This was done to be compatible with the analytical methods that measure the anion in environmental samples. The resultant revised RfD value for perchlorate is 0.0009 mg/kg-day. Confidence in the RfD was designated as medium.

- Pending data on the results of the two-generation reproductive study, immunotoxicity studies, and characterization of perchlorate kinetics and iodide inhibition are expected to impact this assessment. Any risk assessment is an iterative process, and incorporation of new data may require additional evaluation and consideration.

Screening Ecological Risk Assessment

- A secondary acute value of 5 mg/L (as perchlorate) was derived to be protective of 95% of aquatic organisms during short-term exposures with 80% confidence. The secondary chronic value of 0.6 (as perchlorate) likewise was derived to be protective of 95% of aquatic organisms during short-term exposures with 80% confidence. These values were derived based on sodium perchlorate and are probably protective even if ammonium perchlorate is the contaminant released. Calculated ammonia-nitrogen concentrations corresponding to those values are below the acute and chronic ambient water quality criteria for ammonia, regardless of pH.
- For terrestrial plants, the quartile inhibitory concentrations for growth in soil and sand were 78 mg/kg (293 mg/L) and 41 mg/kg (160 mg/L), respectively. A factor of 10 was applied to account for interspecies variance to obtain a screening benchmark of 4 mg/kg.
- Because of limited data on effects for soil invertebrates, a conservative estimate of a threshold for soil community effects was derived at 1 mg/kg. The equivalent aqueous phase benchmark is 2.8 mg/L.
- A factor of 10 for interspecies variance and LOAEL to NOAEL extrapolation was applied to the human health risk LOAEL estimate based on rat data (0.1 mg/kg-day) to obtain a screening benchmark of 0.01 mg/kg-day for the representative herbivore (meadow vole) because it also is a rodent. The population-level implications of this effect are unknown, but it seems likely that such effects on the thyroid could diminish survivorship and fecundity, which would diminish population production.
- No bioaccumulation data are available to indicate whether perchlorate accumulates in animal tissues. Limited data suggest that perchlorate is taken up and concentrated in aerial plant parts, especially leaves. In addition, these studies were phytoremediation studies, so that concentration factors that may result from steady-state could not be estimated.

Uncertainties and Assessment Research Needs

- Accurate exposure information is a requisite for risk characterization for both human and ecological assessments. These data should include transport and transformation processes, notably the fate of perchlorate in irrigated soils because of the potential for evaporative concentration.
- Human health risk research needs include a more accurate linkage between the biologically effective internal dose (e.g., characterization of the dose response for perchlorate inhibition of iodide uptake) in both adult and fetus. More definitive studies of the degree of perturbation of the hypothalamic-pituitary-thyroid axis (i.e., changes in T3, T4, and TSH levels associated with thyroid histopathology), and neurobehavioral effects especially, would improve dramatically the confidence in the assessment. Quantitative interspecies extrapolation requires acute and steady-state characterization of perchlorate toxicokinetics and toxicodynamics.
- Because only a screening tier of tests has been performed, the major uncertainty derives from data gaps. Data on bioaccumulation in aquatic biota would allow evaluation of exposure of organisms that feed on fish and other aquatic organisms. Effects of perchlorate on algae and aquatic macrophytes are required to estimate risks to aquatic primary producers. Data on bioaccummulation in aquatic plants are necessary to assess direct impact to primary consumers (i.e., planktonic and benthic invertebrate communities). Data on accumulation in terrestrial vascular plants also should be investigated further. The factor applied for the use of subchronic data in fish could be addressed by chronic effect testing. Effects also should be determined in nondaphnid invertebrates and of dietary exposure in birds and herbivorous or litter-feeding invertebrates.

Risk Characterization

- As noted above, the lack of exposure information precludes comparison with the human health and ecological toxicity assessment for accurate characterization of risk. Indirect human exposure pathways can be addressed best by a new EPA document, Methodology for Assessing Health Risks Associated with Multiple Pathway of Exposure to Combustor Emissions, which is scheduled for final release in March 1999.
- Perchlorate has caused tumors in rodents only at high exposures for long periods. Noncancer neurobehavioral effects have been shown at lower doses. The estimate for perchlorate has

been based on precursor effects considered protective for both the thyroid neoplasia and neurodevelopmental effects. It is appropriate for comparison against direct oral exposures. The frequency and magnitude of exposure are key attributes for characterization compared with those assumptions of continuous lifetime exposure assumed in the derivation. The degree to which the particular suspected population at risk fits with the assumptions used in the RfD derivation should be kept in mind when performing any risk characterization. Further, RfD estimates are not intended to serve as a "bright line" because, by definition, there is an order-of-magnitude uncertainty around the estimate. This typically translates into a range of threefold below to threefold above the RfD.

- Ecological risk could not be precluded nor accurately characterized because of the significant data gaps described above.

$$\frac{.0009\ \text{mg}}{\text{kg} \cdot \text{day}} \cdot \frac{70\ \text{kg}}{2\ \text{liter}} \cdot \frac{\text{mg}}{\text{liter}}$$

$$\frac{(0.0009)(70)}{(2)}$$

$$31.5\ \text{ppb}$$

$$\frac{\text{mg of chemical}}{\text{kg of body weight} \cdot \text{day}}$$

$$\frac{70 \text{ kg body weight}}{2 \text{ liters of water/day}}$$